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LAG-3, a novel immune checkpoint in Chronic Lymphocytic Leukemia

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Chronic lymphocytic leukemia (CLL) is characterized by an acquired immunosuppression and diminished anti-tumor immunity. Patients with CLL are clear candidates for novel immunotherapies, such as immune checkpoint blockade, that try to restore the patients' immune activity to induce therapeutic responses. Nonetheless, the use of monoclonal antibodies targeting PD-1/PD-L1, which has demonstrated unprecedented clinical efficacy in the treatment of some advanced cancers, has obtained disappointing results in CLL. The profound immune dysfunction of this patients and the role of additional immune checkpoints in this immunosuppression may play a critical role in the low therapeutic response. In agreement, we have characterized novel inhibitory checkpoints, namely LAG-3, ILT2 and HVEM-BTLA, that may be novel therapeutic targets in this malignancy. Particularly, we showed that LAG-3 expression is profoundly dysregulated in CLL and is associated with adverse clinical, genetic and cytogenetics features, and poor outcome of patients. LAG-3 is also involved in the immunosuppression observed in these patients. In line with this, Relatlimab, a new anti-LAG-3 blocking antibody currently in clinical trials in CLL, was able to partially restore NK cell and T cell anti-leukemic activities favoring the depletion of leukemic cells ex vivo. The anti-leukemic effect of Relatlimab may be further potentiated by its combination with the immunomodulatory drug (IMiD) lenalidomide. This drug significantly boosted the activity of T cells and NK cells in CLL having a cooperative effect with Relatlimab in the elimination of leukemic cells. Altogether our data provide a rationale support to further investigate Relatlimab and IMiDs for the management of hematological malignancies.

Biography

Segundo Gonzalez is MD and PhD from University of Oviedo (Spain). He is specialist in Immunology (Central Hospital of Asturias, Spain). He completed his clinical and postdoctoral studies at the Central University Hospital of Asturias, Oviedo, Spain and Fred Hutchinson Cancer Research Center, Seattle, USA. He is Full Professor of Immunology at University of Oviedo and Head of the Tumor Immunology Group at Oncology Institutes IUOPA and Biomedicine Research Institute ISPA. He is a Key Opinion Leader at Beacon Target Therapies (UK)